A MODEL OF GAP JUNCTION CONDUCTANCE AND VENTRICULAR TACHYARRHYTHMIA

X. D. Wu, Y. L. Shen, J. L. Bao, C. M. Cao, W. H. Xu, Q. Xia
Department of Physiology, Zhejiang University School of Medicine, Hangzhou, China
Email: xiaqiang@cmm.zju.edu.cn

Abstract- **Cardiac gap junctions (GJs) form low resistance pathways along which the electrical impulse flows rapidly and repeatedly between all the cells of the myocardium, enabling coordinated contraction of the heart. In many heart diseases, electrical coupling through GJ channels between cardiomyocytes is down regulated. We set up a mathematical model of a chain of myocardial fibers to study how changing the coupling affects the activity of autorhythmic myocytes. While uncoupling blocked the propagation of excitation from autorhythmic myocytes to surrounding quiescent but excitable cells, different degrees of uncoupling increased the automaticity of the cells. Our modeling data suggests that the number of autorhythmic cells plays a key role in the excitation of autorhythmic cells and the conduction of impulses. We conclude that the degree of uncoupling between cardiomyocytes, induced by pathological processes, may generate ectopic foci, tachyarrhythmias being the outcome.**
Keywords **- gap junctions, arrhythmia, computer simulation, intercellular communication**

I. INTRODUCTION

Gap junctions (GJs) contain channels that connect neighboring cells, forming a pathway for the direct exchange of ions and small molecules of up to 1kDa between the cytoplasmic compartments of adjacent cells [1]. In the heart, GJs form low resistance pathways along which the electrical impulse flows rapidly and repeatedly between all cells of the myocardium. Furthermore, GJs form longitudinal and transverse electrical channels on the cell membranes of the cardiomyocytes. The conductance between myocytes varies from 0.25 to 2.5μS [2].

The active and passive properties of plasma membrane channels change in many diseases [2,3]. Abnormal cellular coupling via GJs may induce a series of pathophysiological conditions. In the heart, GJ intercellular communication is the dominant factor in arrhythmogenesis. Decreased GJ coupling between cardiac myocytes may reduce the propagation velocity, and severe uncoupling can block the propagation of the impulse, which facilitates the genesis of reentry arrhythmias [3-5]. On the other hand, in a study with a SA node model cell coupled to a real, isolated ventricular myocyte [6], it was found that reducing the conductance between cells affected the electrical load on the SA model cell, which led to variations in its firing frequency. That means, the coupling state of autorhythmic cells and neighboring cells not only determines the propagation of excitation from the autorhythmic cells to the neighboring quiescent excitable cells, but also affects the autorhythmicity of the autorhythmic cells themselves [2].

In the present study, we used a mathematical model to investigate the effects of altered coupling on the interaction of autorhythmic cells and neighboring myocytes.

II. METHODS

The model contained a variable number (1, 2, 4, 8 or 16) of autorhythmic cells (ARC) as the pacemaker. Forty quiescent but excitable cells (QC) were connected to the ARC (Fig. 1). QCs were represented by the Luo-Rudy dynamic (LRd) model of the mammalian ventricular myocyte [7]. In this model, the action potential was numerically constructed from ionic processes formulated on the basis of experimental data obtained mainly from guinea pig heart. ARCs were constructed according to a slightly modified LRd model, in which an inward current was activated during the phase 4 spontaneous stage to mimic ischemia/reperfusion injury. The basic cycle length of ARC in complete isolation from neighboring cells was 310 ms. GJ conductance between two adjacent ARCs was G_1, and between QCs, G_2. Boundary conductance between ARC and QC was set at G1. G1 and G2 could be varied from 1.2 μS to 0.009375 μS and from 1.2 μS to 0.075 μS, respectively, in different experiments, to mimic the reduced coupling under ischemia/reperfusion conditions. The simulation process was programmed with Visual C++ 6.0, and codes from Dr. Rudy's website were used to modify the single LRd model cell. Computations were run on 7 Pentium-III computers. Action potentials of cells at both ends of the chain were recorded and analyzed with Matlab (Ver. 5.1, The MathWorks, Natick, MA).

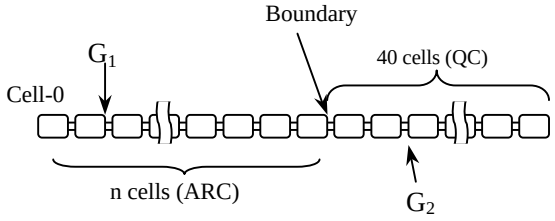

Fig. 1 Schematic of the fiber chain model. Variable number of autorhythmic cells (ARC) (n=1, 2, 4, 8 or 16) interconnected with gap junction conductance G1. Forty quiescent but excitable cells (QC) interconnected with gap junction conductance G2. Boundary conductance between ARC and QC was set at G1.

Report Documentation Page

Report Date	Report Type	Dates Covered (from... to)
25OCT2001	N/A	-

Title and Subtitle A Model of Gap Junction Conductance and Ventricular Tachyarrhythmia	**Contract Number**
	Grant Number
	Program Element Number
Author(s)	**Project Number**
	Task Number
	Work Unit Number
Performing Organization Name(s) and Address(es) Department of Physiology, Zhejiang University School of Medicine, Hangzhou, China	**Performing Organization Report Number**
Sponsoring/Monitoring Agency Name(s) and Address(es) US Army Research Development & Standardization Group (UK) PSC 803 Box 15 FPO AE 09499-1500	**Sponsor/Monitor's Acronym(s)**
	Sponsor/Monitor's Report Number(s)

Distribution/Availability Statement
Approved for public release, distribution unlimited

Supplementary Notes
Papers from the 23rd Annual International conference of the IEEE Engineering in Medicine and Biology Society, October 25-28, 2001, held in Istanbul, Turkey. See also ADM001351 for entire conference on cd-rom.

Abstract

Subject Terms

Report Classification unclassified	**Classification of this page** unclassified
Classification of Abstract unclassified	**Limitation of Abstract** UU

Number of Pages
4

III. RESULTS

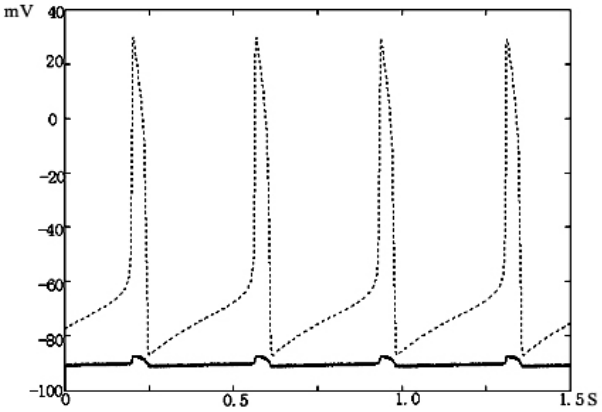

Fig. 2 Membrane potentials of cell-0 (dashed line) and cell-1 (solid line). N was set at 1, cell-0 was an ARC and Cell-1 was a QC. Note that the propagation of excitation from cell-0 to cell-1 was blocked. G1=0.009375μS, G2=1.2uS

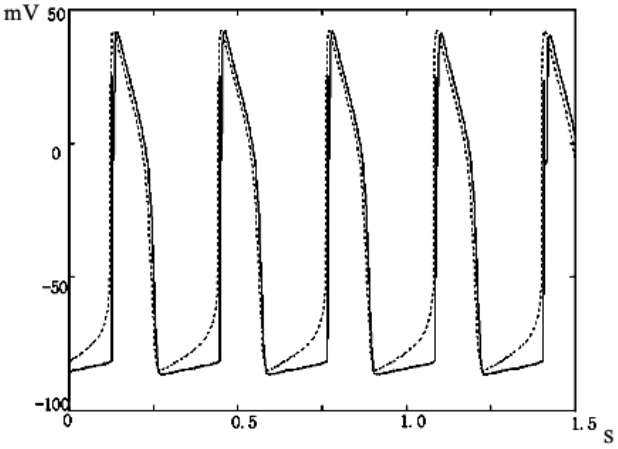

Fig. 3 Membrane potentials of cell-0 (dashed line) and the cell at another end of the chain (solid line). N was set at 16. The action potential conducted through every cell in the chain. G1=0.15μS, G2=1.2μS

When G1 was low (0.009375μS), the action potential in ARC (cell-0) could not propagate(an example is shown in Fig. 2). When G1 was high (0.15μS), the excitation spread from cell-0 and propagated through all cells in the chain (Fig. 3).

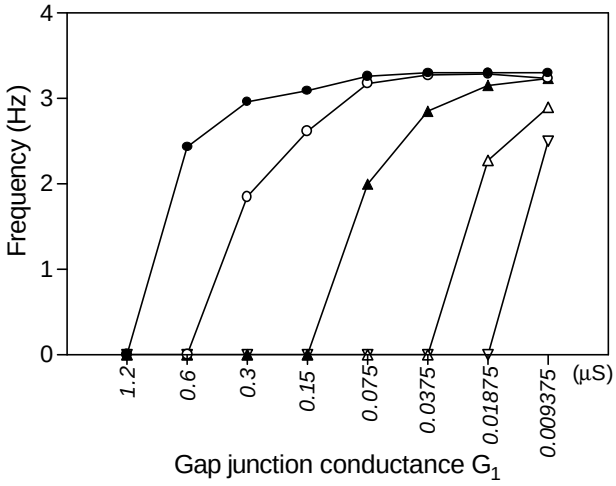

Fig. 4 Relationship between firing frequency of ARC and gap junction conductance G1. ARC number was set to 16 (filled circles), 8 (open circles), 4 (filled triangles), 2 (open triangles) or 1 (inverted triangles). G2=1.2μS, 0 Hz means all cells were at rest.

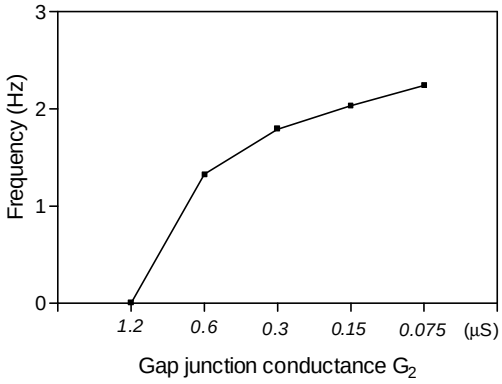

Fig. 5 Relationship between firing frequency of ARC and gap junction conductance G2. N=8 and G1=0.6μS.

The frequency of action potentials initiated in ARC increased with decreasing G1 (Fig. 4). Furthermore, the autorhythmicity of the ARC was suppressed with increasing G1. At the same G1, increasing the number of coupled ARCs elevated the frequency, while at higher G1 the effect of coupled cell number on the frequency was more significant than that at lower G1.

The firing frequency of ARC also increased with decreasing G2 (Fig. 5).

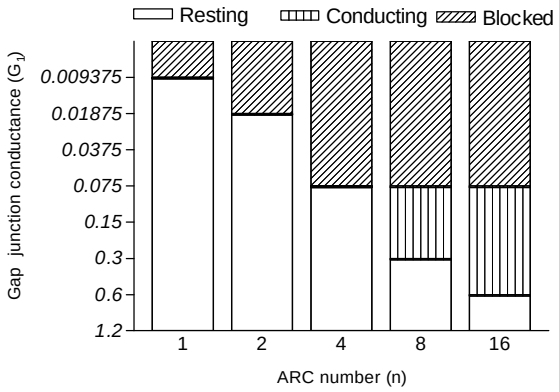

Fig. 6 Effect of ARC number and G1 on the state of the model. Resting: all cells at rest; Conducting: action potential initiated in ARC and propagated to QCs; Blocked: action potential generated in ARC but propagation blocked

The larger the number of ARCs, the greater the initial conductance (G1) between ARCs at which ARCs produced excitation (Fig. 6). The excitation initiated in ARCs at G1 values from 0.075 to 0.6 μS propagated successfully to QC when the number of connected ARCs was 16, and the range of G1 values over which propagation occurred was smaller with 8 than with 16 ARCs.

IV. Discussion

Using a simplified model of the ventricular myocyte, we found that alterations of GJ conductance affected not only the propagation of the action potential but also the autorhythmicity of the pacemaker cardiomyocytes coupled to working ventricular myocytes. Although in the real ventricular myocardium the interactions among cells are more complicated than that in this study, our model provides a useful tool to study the active and passive electrophysiological properties of myocardial fibers.

In the heart, the distribution of GJs is anisotropic, i.e., the densities of GJs differ, depending on the location of the membrane [3,4]. Gap junction channels are found almost exclusively in the intercalated disks at the ends of the cardiomyocytes. The propagation of excitation inside the myocyte mainly spreads along the longitudinal axis of the cell, but can also cross lateral GJ channels. Because of the relative scarcity of lateral GJs, the conduction velocity across lateral GJs is slower. The present model simplified the three-dimensional ventricular myocardium into a one-dimensional chain, ignoring lateral conduction, and provided a linear model with multiple cells for investigating the electrophysiology of myocardial conduction.

In a series of studies, Rudy and co-workers [5] established a single cell model containing almost all the ion channels in the plasma membrane along with their intracellular components, and studied action potential propagation in anisotropic cardiac tissue. In the present study, we used a mathematical model to observe the relationship between GJ conductance and autorhythmicity. Our results are consistent with those of Wagner's group [6], who used a simulated autorhythmic cell coupled to real ventricular myocytes.

In the present study, it was shown that the autorhythmic activity of ARC was released only over a specific range of GJ conductance, i.e., the firing frequency increased with decreasing intercellular conductance, and vice versa. In clinical situations, alterations of cardiac coupling can be induced by ischemia [3,4]. The decreased coupling between cardiomyocytes may result in the elevation of autorhythmicity in pacemaker cells or cells which become autorhythmic under pathological conditions, and finally develop into ectopic foci that induce tachyarrhythmias. On the other hand, the present study showed that when the number of autorhythmic cells was small, ARC could not drive surrounding quiescent cells. This suggests that only one or a few abnormal cells would have little effect, and that the heart's GJs are powerful in buffering the consequences of occasional “mistakes” by cardiac cells.

In conclusion, changes of intercellular communication via GJs may affect both the autorhythmicity and the conductivity of myocardium and consequently play an important role in arrhythmogenesis. Modulation and/or regulation of cardiac coupling by drugs may contribute to the inhibition of tachyarrhythmias. Further studies combining mathematical models with physiological experiments should focus on the role of gap junctions in arrhythmogenesis.

Acknowledgment

We thank Dr. Bruce of the Department of Physiology at the University of Hong Kong for his advice. This work was supported by the Zhejiang Provincial Natural Science Foundation of China (No. 398016, RC99038).

References

[1] N.M. Kumar, N.B. Gilula, “The gap junction communication channel,” *Cell*, vol. 84(3), pp. 381-388, February 1996.

[2] E. Carmeliet, “Cardiac ionic currents and acute ischemia: from channels to arrhythmias,” *Physiol. Rev*, vol. 79(3), pp. 917-1017, July 1999.

[3] N.S. Peters, “New insights into myocardial arrhythmogenesis: distribution of gap-junctional coupling in normal, ischaemic and hypertrophied human hearts,” *Clin. Sci. Colch*, vol. 90(6), pp. 447-452, June 1996.

[4] J.E. Saffitz, “Electrophysiologic remodeling: what happens to gap junctions,” *J. Cardiovasc. Electrophysiol*, vol. 10, pp. 1684-1687, December 1999.

[5] Y. Wang, Y. Rudy, “Action potential propagation in inhomogeneous cardiac tissue: safety factor considerations and ionic mechanism,” *Am. J. Physiol. Heart. Circ. Physiol*, vol. 278(4), pp. H1019-H1029, April 2000.

[6] M.B. Wagner, D. Golod, R. Wilders, E.E. Verheijck, R.W. Joyner, et al, “Modulation of propagation from an ectopic focus by electrical load and by extracellular potassium,” *Am. J. Physiol*, vol. 272(4 Pt 2), pp. H1759-H1769, April 1997.
[7] C.H. Luo, Y. Rudy, “A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes,” *Circ. Res.* vol. 74(6), pp. 1071-1096, June 1994.